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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,227	BUJARD ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's amendment received on 4/1/03 has been entered. Claims 23-34 have been amended. New claims 35-40 have been added. Claims 23-40 are pending and are under current consideration.

Drawings

The drawings filed on 4/1/03are approved.

Election/Restriction

Applicant's affirmation of their election of Group I with traverse is acknowledged in Paper No. 10.

Claim Objections

The previous objections to the claims are withdrawn.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The previous rejection of claims 23-32 under 35 U.S.C. 101 is withdrawn in view of the claim amendments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed invention to the extent of a transgenic mouse, does not reasonably provide enablement for all other transgenic organisms (which are non-human animals in accordance with the elected invention) embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The previous is maintained for the reasons of record advanced on pages 5-12 of the Office action mailed on 1/03/02.

Applicant's arguments filed 4/1/03 have been fully considered but they are not persuasive. Applicants have argued that the tetracycline transcriptional activator (tTA) regulatable system is a highly regulatable and predictable system, which provides a precise mechanism for controlling expression of a gene of interest. Applicants assert that the claimed transgenic non-human animals of the present invention are predictable with respect to phenotype as a result of the tTA system. In particular, Applicants argue that the discussion of Wall, as relied upon by the Examiner, with respect to the unpredictability of transgene expression relating to the "position effect" is not relevant to the instant claims. Applicants assert that the instant invention has solved the "position effect" issue because the transgenic non-human animals embraced by the claims comprise their own transcriptional regulatory system for expressing a gene of interest, which is

regulated by tetracycline (Tc). Applicants submit that a gene of interest is only expressed in the presence of Tc eliminating the unpredictability of when the gene of interest would be expressed. It is of interest to note that Applicants are arguing that a gene of interest is only expressed in the presence of Tc while the claims recite that the expression level of tet operator-linked gene (aka the gene of interest) can downmodulated by administering Tc. See page 12 of the amendment.

In response, the Examiner maintains that the position effect as discussed by Wall can be attributed to unpredictability of transgene expression. Applicant's arguments with regard to Wall appear to be off point because the issue is not relevant to the ability to induce transcription at will. The issue is whether or not transcription will occur at all due to the site of integration of the transgene in the genome. Transcription is mediated by endogenous factors that make up a transcription complex comprised of RNA polymerase and various transcription factors. While tTA system may provide an activating factor that may aid in the recruitment of transcription factors, such an activating factor does not transcribe a gene alone, and neither does Tc as Applicants appear to be arguing. Without the necessary cellular factors transcription of the tet operator-linked gene will not occur. If a transgene of the invention, a tTA system, integrates in a transcriptionally silent genomic region, it can be argued that the necessary cellular factors may not be present in the local microenvironment to facilitate transcription of the tet operator-linked gene. For arguments sake even if a tet operator-linked gene could be expressed at will, no matter where the site of

integration may be, there is no guarantee that the tet operator-linked gene would be expressed at a level resulting in a detectable and functional phenotype. The evidence of record has failed to provide guidance that correlates any site of transgene integration with a phenotype exhibited by a transgenic non-human animal embraced by the claims.

Applicants have argued that Houdebine as recited by the Examiner is not relevant to the instantly claimed invention because the claimed transgenic non-human animals have a controllable system, which is regulated by an exogenous effector molecule and does not rely on endogenous gene sequences. See pages 13-14 of the amendment.

In response, the Examiner asserts that a controllable system such as the tTA system does not ensure that transcription of a gene of interest always occurs no matter where the transgene may integrate. See above. Furthermore, such a controllable system cannot provide a correlation between expression of a gene of interest and a resulting detectable and functional phenotype in a transgenic non-human animal.

Applicants argue with respect to Hammer and Ebert, as cited by the Examiner, that each of these references demonstrates the efficacy of the methodologies taught in the instant specification in the production of transgenic animals. Applicants assert that with respect to Hammer the observation of different phenotypes in transgenic mice and pigs expressing the same transgene is an indication that a transgene designed for one species may not be optimal in another species. See pages 14-15 of the amendment.

In response, the Examiner maintains that a phenotype resulting from expression of a given transgene is unpredictable across species. Both Hammer and Ebert support the unpredictability of phenotypes across species resulting from transgene expression by teaching that expression of the same transgene in transgenic pigs, sheep and mice resulted in different phenotypes. In light of such, it is not possible to predict a phenotype resulting from expression of the same transgene in different animals. Applicants appear to be agreement by arguing that a transgene designed for one species may not be optimal in another species. The evidence of record has provided guidance that correlate to the production of a transgenic mouse comprising a tTA system. However, the evidence of record has not provided guidance that correlates to production of other transgenic non-human animals comprising a tTA system. Moreover, the evidence of record has not provided guidance that correlates a tTa system with the observation of the same phenotypes in different species of non-human animals. As such, the evidence of record has not provided adequate guidance to overcome the unpredictability of a phenotype resulting from expression of a transgene in different species of non-human animals.

Applicants submit the one of ordinary skill in the art would recognize that certain constructs are designed for certain non-human animals, and that this construct may not be appropriate for other types of non-human animals, depending on the transgene. Applicants submit that Mullins as cited by the Examiner discusses the variability of expression of a given construct across species. See pages 15-16 of the amendment.

In response, the Examiner asserts that variability in the expression level of a given construct across species is a major issue of unpredictability with respect to the resulting phenotype as addressed throughout the previous Office action. Accordingly, it is maintained that it is difficult to design transgenes with predictable behavior as discussed above. It appears that Applicants agree that transgene behavior is difficult to predict across species. As such it is maintained that in light of the lack of guidance presented by the specification, which correlates to the creation of transgenic non-human animals other than a mouse, the claims are only enabled to the extent of a transgenic mouse.

Applicants have argued that with respect to the teachings of Kappel it is possible to target a transgene to a particular chromosomal region that is not highly methylated by homologous recombination. See page 16 of the amendment.

In response, the Examiner asserts that the technology of targeting a transgene by homologous recombination to a particular chromosomal region requires the use of embryonic stem cells. It is maintained that such technology is currently limited to the mouse system due to the unavailability of ES cells from other species that contribute to the germline. See pages 10-11 of the Office action mailed on 10/3/02.

Applicants have argued that Strojek and Wagner teach the creation of transgenic non-human animals other than mice. Applicants further argue that the issue of unpredictability of high transgene expression levels in different species is solved by the instant invention. Applicants go to discuss as above, that the tTA

system does not rely on endogenous factors to activate or inhibit gene expression thereby solving the problem of obtaining consistent expression levels of a transgene in a transgenic non-human animal. See pages 16-17 of the amendment.

In response, the Examiner asserts that the evidence of record has not provided guidance that correlates to consistent expression levels of a transgene in species of transgenic non-human animals other than a mouse. As discussed above, a given construct behaves differently across species, which could result in phenotypic differences in non-human animal species that express the same transgene. Furthermore, contrary to Applicants position, and as discussed above, transcription is dependent on the presence of cellular factors that make up the transcription complex regardless of whether transcription can be activated or inhibited by exogenous factors.

Applicants argue that the teachings in the instant specification regarding the construction and use of the Tet repressor-transcriptional inhibitor fusion proteins have been successfully applied in a variety of eukaryotic cell types. Applicants have provided 12 references in support of their assertions that the breadth of the claims is enabled with regard to non-human animals. See pages 17-19 of the amendment.

In response, the Examiner maintains that the transgenic art is unpredictable with regard to a phenotype resulting from transgene expression. See above. None of the 12 cited references addresses the unpredictability of a phenotype resulting from transgene expression in a transgenic non-human

animal as all of the cited references appear to be directed to cultured cells and not transgenic non-human animals.

Applicants argue that non-mouse transgenic non-human animal species have been created. Applicants have provided 4 references that teach the creation of various species of transgenic non-human animals other than mice. See page 19 of the amendment.

In response, the Examiner asserts that the issue is not whether or not transgenic non-human animals other than mice can be created. The issue is whether expression of a tet operator-linked gene will produce a reproducible phenotype when expressed in different species of transgenic non-human animals. See the above discussion.

With regard to the rejection of claims 27-30 for lack of availability of ES cells from species other than mouse, Applicants argue that ES cells are in fact available from other species. Applicants further assert that homologous recombination can occur in species other than mouse. Applicants further assert that some experimentation may be necessary but undue. See *In re Wands*. See pages 19-22 of the amendment.

In response, the Examiner asserts that as of the effective filing date of the invention, that transgene insertion by homologous recombination in transgenic non-human animals was a technology limited to the mouse system due to unavailability of true ES cells from species other than mouse. While putative ES cells have been isolated from species other than mouse, only mouse ES cells have shown germline contribution. Without germline contribution, only chimeric

animals can be produced at best. Chimeric animals cannot be propagated to create transgenic homozygous non-human animals. Chimeric animals only contain small numbers of cells that contain/express the transgene of interest. As such low levels of transgene expression are typical of chimeric animals, wherein it would be unpredictable if a chimeric animal would exhibit a phenotype resulting from transgene expression. Moreover, a chimeric animal does not exhibit reproducible expression levels of transgene expression because the number of ES cells contributing to the germline of a transgenic animal would vary in each case. As such it is maintained that the ES cell technology is undeveloped beyond the mouse. Since the ES cell technology is undeveloped any experimentation required to practice the scope of the invention beyond the mouse cannot be considered routine.

Accordingly, the rejection is maintained for the reasons of record and as discussed above.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 25, 27, 29, 30-31, 33, 35. 37, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites the limitation "the organism" in line 18. There is insufficient antecedent basis for this limitation in the claim. Claims 25, 27, 29, 31, and 33 depend form claim 23.

Claim 35 recites the limitation "the organism" in line 19. There is insufficient antecedent basis for this limitation in the claim. Claims 35 and 37 depend from claim 35.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,859,310. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass transgenic organisms, which are non-human animals in accordance with the elected invention, in particular mice, whose genomes comprise a transgene and a tet operator-linked gene as claimed. The claims of the instant application are directed to a genus of transgenic organisms, which are non-

human animals in accordance with the elected invention, while the claims of US 5,859,310 are directed to transgenic mice, which would anticipate the instant claims.

Furthermore, the transgene comprises a transcriptional regulatory element operatively linked to a polynucleotide sequence encoding a fusion protein that comprises a Tet repressor operably linked to a polypeptide which directly or indirectly activates transcription of said tet operator linked gene. The claims of US 5,859,310 recite a tetracycline-controllable transactivator fusion protein (tTA) while the instant claims recite a fusion protein, which activates transcription of said tet operator linked gene. The specification of the instant application has defined the fusion protein, which activates transcription of said tet operator linked gene, as a tTA fusion protein. See the specification on page 2. In any event in both sets of claims the fusion protein comprises a Tet repressor operatively linked to a polypeptide, which directly or indirectly activates transcription of the tet operator linked gene. Claims 2, 8, and 14 of US 5,859,310 recite that the Tet repressor is a Tn10-derived Tet repressor. The instant specification has defined Tet repressors as encompassing Tn10-derived Tet repressors). See page 2. Finally claims 6 and 12 of US 5,859,310 are directed to methods of inhibiting transcription of the tet operator-linked gene comprising administering tetracycline or a tetracycline analogue. Claim 23 of the instant application meets this limitation by reciting in the last three lines that "the level of expression of the tet operator-linked gene can be downmodulated by administering tetracycline or a tetracycline analogue".

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

PETER PARAS
PATENT EXAMINER

Peter Paras, Jr.

Art Unit 1632